UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

004855

MEMORANDUM:

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. #: 524-308; Roundup; Glyphosate; Pathology Report on Additional Kidney Sections
Caswell No. 661A
Accession No. 259621

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)

THRU: Robert P. Zendzian, Ph.D. 12/12/85
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D. William Dykstra 12/12/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

12/12/85

Requested Action:

Review pathology report on additional kidney sections.

Background:

Glyphosate was considered oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner. The incidence of this tumor was 0, 0, 1, and 7 in the control, low-, mid-, and high-dose groups, respectively.

Additional evaluation of all original renal sections identified a small renal tubular adenoma in one control male (animal No. 1028) which was not diagnosed as such in the original pathology report.

Subsequently, Toxicology Branch recommended that additional renal sections be cut and evaluated from all control and glyphosate treated male mice.

This review contains the evaluation of the submitted results of the additional sectioning and pathological data.

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Conclusion:

The results of the additional pathological evaluation on re-cut kidney sections in male mice demonstrated no additional tumors were present. The significance of this finding will be determined later by the Ad Hoc committee.

Review:

1. The pathology report of additional kidney sections submitted by the registrant (Monsanto) showed that the renal tubule adenoma incidence in male mice was as follows:

Dose (ppm)	0	1000	5000	30,000
Animal number			3023	4029,4032,4041
Renal tubule adenoma	0	0	1	3
No. examined	49	49	50	50

The additional tumor in the control group which had been diagnosed from the re-evaluation of the original slides was not present in the re-cut kidney sections.

Toxicology Branch's pathologist (report attached) stated that the control tumor "does not represent a pathophyioloically significant change".

Statistical analysis of the tumor results showed no significant ($P<0.05$) difference in the incidence of renal tubule adenoma between control and treated groups.

However, the test for linear trend in proportions resulted in a $p=0.016$ which is statistically significant.

According to the registrant's pathology report, non-neoplastic kidney lesions did not reveal evidence of an ongoing chemically induced neprotoxicity.

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Based on the original report and the new report, Toxicology Branch concludes that chronic interstitial nephritis occurred in compound-related manner in males at the high-dose as is shown below:

Males (Chronic Interstitial Nephritis)				
Dose (ppm)	0	1000	5000	30,000
Incidence				
Original report	5/49	2/49	7/50	12/50
New report	5/49	1/49	7/50	16/50

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 4, 1985

004855

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: William Dykstra, Ph.D.
Reviewer, Toxicology Branch, TS-769

FROM: Louis Kasza, D.V.M., Ph.D. L K
Pathologist, Toxicology Branch, TS-769

SUBJECT: Glyphosphate -- Evaluation of Kidney Tumors in Male Mice.
Chronic Feeding Study.

INTRODUCTION:

Tumors (0 (1)*; 0; 1; 3) were found in the kidneys of male mice at different dose levels. There were differences in the pathologists' opinions as to whether the small localized change in one kidney of the control group (#1028) represented a tumor or not. In order to provide more information, the Agency recommended the preparation of three (3) additional sections from each kidney in the male groups. "The lesion was not present in the recut specimens from that animal" in the control group (#1028). In the final re-evaluation of the questionable control kidney slides (#1028), the conclusion was formulated that "The pathology staff at Bio/dynamics and I (Dr. McConnell) reviewed the lesion and concur that it may be representative of a developing tumor".

MATERIALS AND METHODS:

I (Dr. Kasza, Branch Pathologist) requested all kidney sections from male mice. After selection of slides from all animals in which kidney tumors were diagnosed, I studied them under the microscope.

RESULTS:

There was no difference in diagnoses between my and other pathologists' diagnoses with respect to kidney tumors in mid- (#3023) and high dose (#4029, 4023, 4041) groups. With regard to the questionable male control kidney (#1028), it is my opinion that the presence of a tumor can not definitely be established. My interpretation is similar to the conclusion of Bio/dynamics' pathology staff and Dr. McConnell, that the lesion "may be" a proliferative change having the potential to lead to the development of a frank tumor. But as the tissue can be seen under the microscope as a small well-demarcated focal cell aggregate morphologically different from the healthy looking surrounding kidney tissue, this morphological alteration does not represent a pathophysiologically significant change.

*In parentheses is the review pathologist's findings.

cc: T. Farber
W. Burnam
R. Engler
R. Zendzian

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Test for Significance of Differences Between Proportions 11/13/85

renal tubule adenoma mice

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ppm	# RESP	Total	%	+/-2(S.E.)	One Tail P Statistic Fisher's
0.000	1	49	2.04	+/-(4.56)	
1000.000	0	49	0.00	+/-(1.02)	$$$$$
5000.000	1	50	2.00	+/-(4.88)	$$$$$
30000.000	3	50	6.00	+/-(7.58)	0.310

This linear trend test often gives incorrect results

Test for a linear trend is not significant

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Test for Significance of Differences Between Proportions 2/11/85

renal tublule adenoma ,male mice

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ppm	# RESP	Total	%	+/-2(S.D.)	One Tail P Statistic Fisher's
0.000	0	49	0.00	+/-(1.02)	
1000.000	0	49	0.00	+/-(1.02)	$$$$$$
5000.000	1	50	2.00	+/-(4.88)	0.505
30000.000	3	50	6.00	+/-(7.58)	0.125

This linear trend test often gives incorrect results

Test for Linear Trend in Proportions P = 0.016

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END